(Rel.82A—12/99 Pub.60S) FORM 13-6

Practitioner's Docket No. R00282US (#90568) **PATENT**

Preliminary Classification:

Proposed Class:

Subclass:

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.'" M.P.E.P. § 601, 7th ed.

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE (DO/US)— ENTRY INTO THE U.S. NATIONAL STAGE UNDER CHAPTER I

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/07900	14 AUGUST 2000	25 AUGUST 1999

TITLE OF INVENTION THERAPEUTIC SYSTEM CONTAINING AN ACTIVE SUBSTANCE FOR THE APPLICATION ON THE SKIN WHICH CONTAINS AT LEAST TWO POLYMEROUS LAYERS

APPLICANT(S)

BERTHOLD, Achim

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231

ATTENTION: DO/US

NOTE: The completion of those filing requirements that can be made at a time later than 20 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 U.S.C. § 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase. See 37 C.F.R. § 1.491, which states: "An international application enters the national stage when the applicant has filed the documents and fees required by 35 USC 371(c) within the periods set forth in § 1.494 and § 1.495."

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date APRIL 24, 2001, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number EL148508007US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

KATHERINE R. VIEYRA
(type or print name of person mailing paper)

Katherine R. Vieyra
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

WARNING: *Where the items are those that can be submitted to complete the entry of the international application into the national phase subsequent to 20 months from the priority date, the application is still considered to be in the international stage. And if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (because international application papers are not covered by an ordinary certificate of mailing. 37 C.F.R. § 1.8(2)(xi)).*

WARNING: *Documents and fees must be clearly identified as a submission to enter the national stage under 35 U.S.C. § 371, otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).*

WARNING: *Failure to pay the national fee within 20 months from the priority date will result in the abandonment of the application. The time for payment of the basic fee is not extendable. M.P.E.P. § 1893.01(a)(1), 6th ed., rev. 3.*

1. Applicant herewith submits to the United States Designated Office (DO/US) the following items under 35 U.S.C. § 371:

a. ☑ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and

☒ other fees (37 C.F.R. § 1.492), as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
N*	TOTAL CLAIMS	6 —20=	---	×$ 18.00=	$ ---
	INDEPENDENT CLAIMS	2 —3=	---	×$ 78.00=	---
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	---
BASIC FEE**	The international search fee, as set forth in § 1.445(a)(2) to be paid to the US PTO acting as an International Searching Authority: ☐ has been paid (37 CFR 1.492(a)(2)) ..... $690.00 ☐ has not been paid (37 CFR 1.492(a)(3)) ..... $970.00 XXXX where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $860.00				$ 860.00
	Total of above Calculations				= 860.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed also. (note 37 CFR 1.9, 1.27, 1.28) (Large)				– ---
	Subtotal				860.00
	Total National Fee				$ 860.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See item 10 below). See attached "ASSIGNMENT COVER SHEET (37 C.F.R. § 3.34)".				---
TOTAL	Total Fees enclosed				$ 860.00

* See attached Preliminary Amendment Reducing the Number of Claims.

***WARNING:** *"To avoid abandonment of the application, the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 20 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 20-month time limit may not be extended." 37 C.F.R. § 1.494(b).*

i. ☒ Credit Card Payment Form
A ~~check~~ in the amount of $ 860.00--- to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of $ _____.

A duplicate copy of this sheet is enclosed.

WARNING: If the translations of the international application and/or the oath or declaration have not been submitted by the applicant within twenty (20) months from the priority date, the applicant will be so notified and given a period of time within which to file the translation and/or oath or declaration in order to prevent abandonment. The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than twenty (20) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than twenty (20) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 will apply. 37 C.F.R. § 1.494(c).

3. A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

a. ☒ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☐ has been transmitted

i. ☐ by the International Bureau. Date of mailing of the application (from form PCT/IB/308): _____.

ii. ☐ by applicant on _____ Date

NOTE: Section 1.494(b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 20 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies the applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage and applicant has received notice from the International Bureau, applicant need only pay the basic national fee by 20 months from the priority date." [This can now be paid subsequently with a surcharge.] Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35.

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☒ is transmitted herewith.

b. ☐ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____ Date

5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: *The Notice of January 7, 1993 indicates that 37 C.F.R. § 1.494(d) was "amended to clarify the existing practice that PCT Article 19 Amendments must be submitted by 20 months from the priority date, which time may not be extended." This Notice further advises: "Of course, the failure to do so does not result in loss of the subject matter of PCT Article 19 amendments. The applicant may submit that subject matter in a preliminary amendment filed under Section 1.121. In many cases, filing an amendment under Section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 35. See item 11(c) below. See also 37 C.F.R. § 1.494(d).*

a. ☐ are transmitted herewith.

b. ☐ have been transmitted

i. ☐ by the International Bureau. Date of mailing of the amendment (from form PCT/IB/308): _____.

ii. ☐ by applicant on _____ Date

c. ☒ have not been transmitted, as

i. ☐ no notification has been received that the International Search Authority has received the Search Copy.

ii. ☐ the Search Copy was received by the International Searching Authority, but the Search Report has not yet been issued. Date of receipt of Search Copy (from form PCT/ISA/202): _____.

iii. ☒ applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210): 10 APRIL 2001.

iv. ☐ the time limit for the submission of amendments has not yet expired. The amendments, or a statement that amendments have not been made, will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the amendments were made in the English language.

c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ An oath or declaration of the inventor, including power of attorney, (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. ☐ was previously submitted by applicant on _____ Date

b. ☐ is submitted herewith, and such oath or declaration

i. ☐ is attached to the application.

ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or (c) and 5(b); and states that they were reviewed by the inventor, as required by 37 C.F.R. § 1.70.

iii. ☒ will follow.

Other document(s) or information included:

8. ☒ An international Search Report or Declaration under PCT Article 17(2)(a):
   a. ☒ is transmitted herewith.
   b. ☐ has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____.
   c. ☐ is not required, as the application was searched by the United States International Searching Authority.
   d. ☐ will be transmitted promptly upon request.
   e. ☐ has been submitted by applicant on _____ Date
   f. ☐ is not transmitted, as the international search has not yet issued.
9. ☒ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:
   a. ☐ is transmitted herewith.
      Also transmitted herewith is (are)
      ☐ Form PTO—1449 (PTO/SB/08A and 08B)
      ☐ Copies of citations listed
   b. ☒ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).
   c. ☐ was previously submitted by applicant on _____ Date
10. ☐ An assignment document is transmitted herewith for recording. A separate
    ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or
    ☐ FORM PTO—1595
    is also attached.
    ☐ Please mail the recorded assignment document to:
    i. ☐ the person whose signature and address appears below.
    ii. ☐ the following:

09/830300

JC03 Rec'd PCT/PTO 24 APR 2001

11. ☒ Additional documents
    a. ☐ Copy of request (PCT/RO/101)
    b. ☒ International Publication No. WO 01/13899
        i. ☐ Specification, claims and drawing
        ii. ☒ Front page only
    c. ☒ Preliminary amendment (37 C.F.R. § 1.121)
    d. ☐ Other

12. ☒ The above checked items are being transmitted
    a. ☐ before the 18th month publication.
    b. ☒ after publication and the article 20 communication, but before 20 months from the priority date.
    c. ☐ after 20 months (revival).

NOTE: Petition to revive (37 C.F.R. § 1.137(a) or (b)) is necessary if 35 U.S.C. § 371 requirements are submitted after 20 months.

13. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____ (Date) namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 08-2441.

☒ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 20 months without extension (37 C.F.R. § 1.494(b)(2)), results in abandonment of the application, it would be best to always check the above box.*

☒ 37 C.F.R. § 1.492(b), (c), and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment, prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

☒ 37 C.F.R. § 1.17 (application processing fees)

☒ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a)).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b)).

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying or at the time of paying . . . issue fee. . .." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☒ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 20 months after the priority date.

Signature of practitioner

Reg. No. 24,603

D. PETER HOCHBERG

(type or print name of practitioner)

Tel. No.: (216) 771-3800

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P.O. Address

Customer No.: 28,672

CLEVELAND, OH 44114-2294

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Achim Berthold

Serial No. :

Filed : (Herewith)

Title : THERAPEUTIC SYSTEM CONTAINING AN ACTIVE SUBSTANCE FOR THE APPLICATION ON THE SKIN WHICH CONTAINS AT LEAST TWO POLYMEROUS LAYERS

Attorney File : RO0282US (#90568)

Box PCT
Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to substantive examination of the above-identified application, please amend the application, without prejudice, as follows:

In the Specification:

Page 12, after the last paragraph, insert the following paragraph:

-- The invention has been described with particular emphasis on the preferred embodiments, but variations and modifications within the spirit and scope of the invention may occur to those skilled in the art to which the invention pertains. --

In the Claims:

Please delete claim 6.

1. (Amended) Active substance-containing therapeutic system for application on the skin, comprising at least two polymer-containing layers, wherein the polymers used for the different layers differ in their glass transition temperature.

2. (Amended) Therapeutic system according to Claim 1, wherein one of the layers contains a high-molecular polymer which has film-forming properties.

3. (Amended) Therapeutic system according to Claim 1, wherein one of the layers is formed to simultaneously serve as a control means for active substance release.

4. (Amended) Therapeutic system according to Claim 1, wherein one of the layers is formed and arranged as an active substance reservoir.

5. (Amended) Process for manufacturing the therapeutic system according to Claim 1, comprising:

laminating at least two polymer-containing layers upon each other, said layers containing polymers that differ in their glass transition temperature.

7. (New) A method for providing therapeutic applications in human medicine, said method comprising the step of applying to living skin an active substance-containing therapeutic system, the system having at least two polymer-containing layers, wherein the polymers for effecting the therapeutic system in the respective layers differ in their respective glass transition temperatures.

REMARKS

The English translation of the specification submitted herewith has headings inserted into it to enhance clarity and conformance with U.S. patent practice, but otherwise is an accurate translation of the original specification. Similarly, the foregoing amendments to the claims, including deleting the reference numbers, are made to place them in conformance with U.S. patent practice and to delete multiple-dependencies, thus reducing the government filing fee. A

marked up version of the original amended claims is attached. Accordingly, prosecution on the merits hereof is respectfully requested.

Respectfully submitted,

By: _____
D. Peter Hochberg
Reg. No. 24,603

DPH/ KRV/ Enc. and Attachment: Marked Up Claims

D. Peter Hochberg Co., L.P.A.
The Baker Building - 6th Floor
1940 East 6th Street
Cleveland, Ohio 44114
(216) 771-3800

EXPRESS MAIL CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that the foregoing Preliminary Amendment and any document(s) referred to as attached hereto is being deposited with the United States Postal Service on the date indicated below in an envelope as "Express Mail Post Office to Addressee" service mailing Label Number EL148508007US addressed: Box PCT, Commissioner for Patents, Washington, D.C. 20231.

Date: April 24, 2001

Katherine R. Vieyra

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Achim Berthold
Serial No.	:	
Filed	:	(Herewith)
Title	:	THERAPEUTIC SYSTEM CONTAINING AN ACTIVE SUBSTANCE FOR THE APPLICATION ON THE SKIN WHICH CONTAINS AT LEAST TWO POLYMEROUS LAYERS
Attorney File	:	RO0282US (#90568)

ATTACHMENT TO PRELIMINARY AMENDMENT

MARKED UP CLAIMS SHOWING CHANGES RELATIVE TO THE ORIGINAL VERSION

Please delete claim 6.

1. (Amended) Active substance-containing therapeutic system for application on the skin, comprising at least two polymer-containing layers, [characterized in that] wherein the polymers used for the different layers differ in their glass transition temperature.

2. (Amended) Therapeutic system according to Claim 1, [characterized in that] wherein one of the layers contains a high-molecular polymer which has film-forming properties.

3. (Amended) Therapeutic system according to Claim 1 [or 2], [characterized in that] wherein one of the layers is formed to simultaneously serve as a control means for active substance release.

4. (Amended) Therapeutic system according to [one or more of the preceding claims] Claim 1, [characterized in that] wherein one of the layers is formed and arranged as an active substance reservoir.

5. (Amended) Process for manufacturing the therapeutic system according to [any one of the preceding claims] Claim 1, [characterized in that] comprising:

laminating at least two polymer-containing layers [are laminated] upon each other, said

layers containing polymers that differ in their glass transition temperature.

THERAPEUTIC SYSTEM CONTAINING AN ACTIVE SUBSTANCE FOR THE APPLICATION ON THE SKIN WHICH CONTAINS AT LEAST TWO POLYMEROUS LAYERS

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to an active substance-containing therapeutic system for application to the skin comprising at least two polymer-containing layers. The invention further relates to a manufacturing process as well as to a use of the therapeutic system.

Description of the Prior Art

The pharmaceutical preparation for delivery of active substances to the skin aims either at a transdermal systemic action or at a dermal, local action of the active substances released. Adherence to the application surface is secured through adhesives forming high-viscous, permanent-adhesive structures. Here, quality characteristics such as initial tackiness (tack), adhesive power (adhesion) and internal strength of the pressure-sensitive adhesive (cohesion) are distinguished.

The pharmaceutical preparation is an active substance-containing device which releases one or more medicinal agents at a predeterminable rate, continuously, over a defined period of time, to a defined site. Such a device is characterized by an exact plan of treatment, called dosage plan, and is called a therapeutic system (TS). As the systems according to the present invention are stuck to the skin as patches to obtain either a systemic or a local effect, these systems are referred to in the given context as transdermal therapeutic systems (TTSs) or as dermal therapeutic systems (DTSs).

The preparation according to the present invention has a high degree of efficacy. This means that the preparation leads to high bioavailability of the active substances. Action can be broken off at any time by the simple removal of the preparation. As a consequence, the preparation is characterized also by controllability of the active substance release. The preparation according to the invention furthermore has high reliability with regard to patients' observing the therapeutic plan (so-called compliance) since the frequency of application is greatly reduced as compared to conventional drug forms, and side effects occur only rarely. Further, the amount of active

substance to be applied can, as a rule, be reduced. Thus, dose-dependent side effects are likewise reduced or avoided. This results in increased therapeutic safety.

Usually, an active substance-containing system, TTS or DTS, comprises an assembly of a plurality of layers comprising at least one active substance- and/or auxiliary substance-containing reservoir layer, a backing layer impermeable to the ingredients of the latter, and a protective layer to be removed prior to application to the skin.
The reservoir layer here consists as a rule of an amorphous polymer containing active substances and/or auxiliary substances. Apart from a number of advantageous properties of the polymer, especially with regard to its use as patches, such as diffusion-dependent absorption or release of the ingredients, or their flexibility in conforming to a given shape of the body at the application site, amorphous polymers on the other hand tend to show cold flow in the patch, especially in the case of prolonged storage, as a consequence of comparatively insufficient cohesion.

Whereas in pure-crystalline substances, at the melting point the molecular motion increases rapidly from a relatively low level to a high level with increasing

temperature, amorphous polymers such as adhesives behave differently.

As the temperature increases, molecular movement increases in several reversible stages, mostly 5 different ones. In detail, five ranges of viscoelasticity are distinguished as glassy state (hard; lowest temperature), leathery state (turning point = glass transition temperature (Tg) = temperature at which a polymer changes from the solid glassy state to the rubber-elastic state), rubber-elastic state, rubber-elastic flow, and viscous state (highest temperature).

The transition from glassy state to the rubber-like state is accompanied by a marked change in the physical properties such as specific volume, modulus of elasticity, heat capacity, thermomechanic properties and refractive index. The melting point (Tm; solid and liquid polymer are balanced) of amorphous polymers is defined by partially crystalline polymer regions. Here, Tg is always below Tm.

Distinctions are made between:

Polymers which at room temperature (TA) are in the solid glassy state, with Tg, TM > Ta. Examples are isotactic polystyrene: Tg = 85 °C / Tm = 240 °C; polyethylene terephthalate: Tg = 69 °C / Tm = 265 °C; polyhexamethylene

adipamide: Tg = 53 °C / Tm = 265 °C;
polytetrafluoroethylene: Tg = 126 °C / Tm = 325 °C).
Polymers which are in the soft rubberlike intermediate state (Tm > Ta > Tg). Examples are high-density polyethylene: Tg = -70 °C / Tm = 139 °C; isotactic polypropylene: Tg = -18 °C / Tm = 186 °C.
Polymers which are in the liquid viscous state (Ta > Tm, Tg; examples are polydimethyl siloxane: Tg = -121 °C / Tm = -40 °C; 1,4-cis-polybutadiene: Tg = -95 °C / Tm = 2 °C).

It can be derived from this that the cohesion and thereby the cold flow of an adhesive having high-viscous, permanent-adhesive polymer structures is decisively influenced by the glass transition temperature of the polymers employed.

Cold flow describes a property of a material. The materials affected by this start to flow during storage without having been subjected to special influences, consequently they can be considered high-viscous liquids.

It is known from practice that TTSs and DTSs often tend to show cold flow. This leads to a patch becoming agglutinated with the primary packing means while it is being stored so

that it can be removed subsequently only with difficulty. A further problem consists in that after application the patches leave black margins, residues of adhesive, on the surface of application which in part can be removed only by means of intensive cleaning measures.

WO 86/00814 as well as US 5,186,938 describe the possibility of improving the cold flow in glycerol trinitrate-containing, self-adhesive, polyacrylic acid-derived polymers by crosslinking the polymers. For crosslinking, divalent metal ions or melamine are used, for example. This creates a coherent network that has a considerably lower tendency for cold flow than the starting polymer. Cross-linkage, which has a positive effect on cohesion, has, on the other hand, a negative influence on tack, which thereby deteriorates.

The latter is a universal rule of thumb. The inventors of the known method attempt to solve the problem by using the agent that brings about the cross linkage only in a relatively small amount in order to ensure a minimum tack. The problem with the procedure described by the inventors is that the degree of cross linkage must be adjusted accurately to guarantee optimum system properties.

To be independent from the sensitivity of cohesion and tack, which is dependent on the degree of cross link, a different procedure is proposed in EP 0 856 311 A1 and DE 197 06 824 C1. To improve the cohesion of the matrix without reducing the adhesive power on the skin, systems are proposed which consist of at least two layers. The special aspect here is that the layers although having the same polymer composition and the same concentration of dissolved ingredients, differ in the degree of cross linkage. While a layer with a lower degree of cross link ensures adhesion to the skin, another layer, having a higher cross link degree, reduces cold flow. Cross-linking is carried through in a known manner, for example, by addition of metallic ions or reactive reagents as well as by electron irradiation or irradiation with ultraviolet light.

Another possibility to improve cohesion is known from DE 40 20 144 C2. This document describes a possibility of improving cold flow without the use of reagents for cross-linking. To this end, a further non-adhesive but film-forming polymer is added to the self-adhesive base polymer. This film-forming polymer, which is typically characterized

by a high molecular weight, results in a considerable improvement of cohesion.

The above-described processes for improving cohesion cannot be employed in all cases. For example, not all polymers which are adhesive and are thus suitable for the production of self-adhesive TTSs or DTSs can be crosslinked. Also, admixture of cohesion-enhancing polymers is not always possible, for reasons of compatibility.

SUMMARY OF THE INVENTION

Starting from the aforementioned state of the art, it is the object of the invention to provide a process for improving cohesion in order to achieve a clear reduction of the cold flow, which process, at least for the most part, overcomes the difficulties and technical limits observed heretofore and leads to a high bioavailability of the active substances and auxiliary substances contained.

Description of the Preferred Embodiment

This object is achieved with an active substance-containing therapeutic system for application on the skin comprising at least two polymer-containing layers, by a layered structure of the TTS or DTS.

The various layers differ in their glass transition temperature (Tg). The layer(s) with the higher glass transition temperature(s) lead(s) to an improvement of the cohesion of the entire system. As a consequence, cold flow is reduced, so that the problem of TTSs or DTSs becoming agglutinated with the primary packaging means during storage and leaving black edges on the application surface owing to residues of adhesive does no longer appear or is strongly reduced. Furthermore, incompatibilities are avoided by the fact that the polymers used are present in different layers, so that their interaction is substantially restricted to the interfaces. In favourable cases one can dispense with cross-linking.

Further embodiments are described in accordance with the subclaims.

One of the layers can simultaneously be provided as a control means for active substance release.

The process according to the invention further provides for at least one of the layers to be formed and arranged as an active substance reservoir.

Finally, a process for the manufacture of the therapeutic system comprises the steps of laminating at least two polymer-containing layers upon one another, with the layers containing polymers which differ in their glass transition temperature.

A use of the therapeutic system according to the inventions serves the topical or transdermal release of active substances to the skin of an organism.

An exemplary, schematic representation of the system according to the invention can be seen from Figure 1. This shows an embodiment example consisting of five layers (a to e). The layers are:

a) backing layer,
b) matrix 1a with a polymer designated as Tg1,
c) matrix 2 with a polymer designated as Tg2,
d) matrix 1b with a polymer designated as Tg1,
e) protective layer, detachable, with Tg2 > Tg1.

Example:

To prepare the matrix 1a, 25.0 g of a polymer based on methacrylic acid (Eudragit® L100) are dissolved in 16.1 g of ethanol. After complete dissolution of the methacrylic

acid polymer, to this pre-solution were added the active substances estradiol (925.0 mg) and norethisterone acetate (5.25 g), and this was again stirred until the active substances were dissolved. Thereafter, 38.84 g of an adhesive solution (solution of a self-adhesive polymer based on polyacrylic acid esters in ethyl acetate, 51.0%-wt.; Durotak® 387-2287), 11.50 g of a tack-imparting resin (Hercolyn® D), 7.5 g of glycerine, as well as 6.0 g of a solution of aluminium acetyl acetonate in ethyl acetate (4%-wt.) were successively added and subsequently homogenised. The resultant mass had a solids content of 45%-wt. This mass was then applied to a siliconized polyester film (Hostaphan® RN100) by means of a film casting instrument, at a layer thickness of 250 µm, and dried under defined conditions (30 min at 50 °C). The dried film was covered with a flexible polyester film (Hostaphan® RN15), which represented the later backing layer. Matrix 1b was prepared in an analogous manner, with the difference that the final covering with a flexible polyester film was left out. To prepare matrix 2, 30.0 g of a high-molecular polymer based on methacrylic acid ester (Plastoid® B) in ethyl acetate were initially dissolved in ethyl acetate, so that a 30%-wt. solution resulted. This solution was then

applied to a siliconized polyester film (Hostaphan® RN100) by means of a film casting instrument, at a layer thickness of 250 µm, and dried under defined conditions (30 min at 50 °C).

When the dried matrices had been obtained, the siliconized polyester film was removed from matrix 1a and the matrix laminated on matrix 2. Then, the siliconized polyester film was removed from matrix 2 and the matrix laminated with matrix 1b. The result was a system comprising the layers: a) backing layer (Hostaphan® RN15), b) matrix 1a, c) matrix 2, d) matrix 1b, and e) protective layer (Hostaphan® RN100). The system is schematically shown in Fig. 1.

To assess the cold flow, the mentioned formulations and a formulation which contained only the matrices 1a and 1b were stored under defined conditions (40 °C, 75% relative humidity). The laminate without matrix 2 showed strong cold flow already after one month. By contrast, such cold flow was not observed in the laminate comprising matrix 2.

C L A I M S

1. Active substance-containing therapeutic system for application on the skin, comprising at least two polymer-containing layers, characterized in that the polymers used for the different layers differ in their glass transition temperature.

2. Therapeutic system according to Claim 1, characterized in that one of the layers contains a high-molecular polymer which has film-forming properties.

3. Therapeutic system according to Claim 1 or 2, characterized in that one of the layers is formed to simultaneously serve as a control means for active substance release.

4. Therapeutic system according to one or more of the preceding claims, characterized in that one of the layers is formed and arranged as an active substance reservoir.

5. Process for manufacturing the therapeutic system according to any one of the preceding claims, characterized in that at least two polymer-containing layers are

laminated upon each other, said layers containing polymers that differ in their glass transition temperature.

6. The use of the therapeutic system according to any one of the preceding claims for topical or transdermal release of active substances to the skin of an organism.

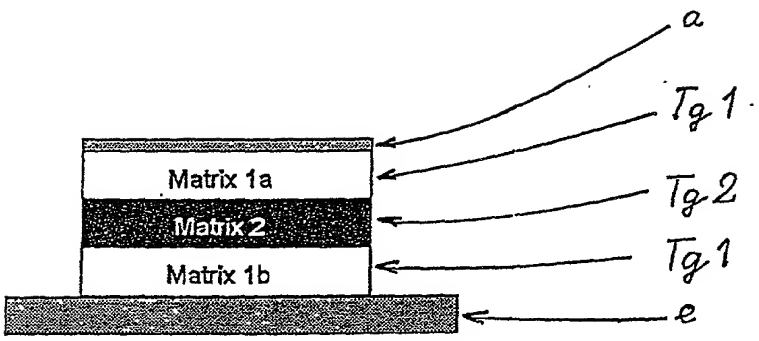

FIG. 1

"Kalker Flab, Holländerin"

Attorney Docket No. **RO0282US (#90568)**

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL,CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: (check one applicable item below)

( ) original
( ) design

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application do not check any of next two items and check appropriate one of last three items.

(X) national stage of PCT
( ) supplemental

NOTE: If one of the following 3 items apply then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR CIP.

( ) divisional
( ) continuation
( ) continuation-in-part (CIP)

INVENTORSHIP IDENTIFICATION

My residence, post office address and citizenship are as stated below next to my name, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

THERAPEUTIC SYSTEM CONTAINING AN ACTIVE SUBSTANCE FOR THE APPLICATION ON THE SKIN WHICH CONTAINS AT LEAST TWO POLYMEROUS LAYERS

SPECIFICATION IDENTIFICATION

the specification of which: (complete (a), (b), or (c))

(a) ( ) is attached hereto.
(b) (X) was filed on as ( ) Serial No. or
(X) Express Mail No. EL148508007US on April 24, 2001, as Serial No. not yet known and was amended on (if applicable).

(c) (X) was described and claimed in PCT International Application No. **PCT/EP00/07900** filed on **August 14, 2000** and as amended under PCT Article 19 on (if any).

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations. Sec. 1.56(a).

( ) In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.97.

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) ( ) no such applications have been filed.
(e) (X) such applications have been filed as follows

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

COUNTRY	APPLICATION NO.	DATE OF FILING (month,day,year)	PRIORITY CLAIMED UNDER 37 USC 119
			( ) YES NO ( )
			( ) YES NO ( )
			( ) YES NO ( )

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

German Appln. 199 40 238.8 filed August 25, 1999
and
PCT Appln. PCT/EP00/07900 filed August 14, 1999

POWER OF ATTORNEY

As a named inventor, I hereby appoint D. Peter Hochberg, Reg. No. 24,603, Katherine R. Vieyra, Reg. No. 47,155, and William H. Holt, Reg. No. 20,766, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:	DIRECT TELEPHONE CALLS TO: (Name and telephone number)
D. Peter Hochberg Co., L.P.A. 1940 East 6th Street - 6TH Floor Cleveland, Ohio 44114-2294	D. Peter Hochberg (216) 771-3800

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full name of **sole or first inventor: Achim Berthold**

Berthold
Inventor's signature

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Date — Country of Citizenship

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_____

Inventor's signature

_____

Date Country of Citizenship

_____

Residence

_____

Post Office Address

CHECK PROPER BOX(ES) IF ANY OF THE FOLLOWING ADDED PAGE(S) FORM A PART OF THIS DECLARATION

( ) Signature for third and subsequent joint inventors. Number of pages added _____ .

( ) Signature by administrator(trix), executor(trix) or legal representative of deceased or incapacitated inventor. Number of pages added _____ .

( ) Signature for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR 1.47. Number of pages added _____ .

***

( ) Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (CIP) application.

( ) Number of pages added _____ .

***

If no further pages form a part of this Declaration then end this Declaration with this page and check the following item.

(X) This declaration ends with this page.